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(54) Title: ENHANCED BIOAVAILABILITY PHARMACEUTICAL COMPOSITION CONTAINING PROBUCOL

(57) Abstract

A pharmaceutical composition of probucol that both enhances bioavailability of the drug and reduces plasma drug level variability in a patient population comprising a therapeutically effective amount of probucol dissolved in a propylene glycol ester of fatty acids wherein the fatty acids are selected from the group consisting of the fatty acids represented by $C_xH_{2x}O_2$, wherein x is 4, 6, 8, 10, 12, 14, 16.

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+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

ENHANCED BIOAVAILABILITY PHARMACEUTICAL COMPOSITION CONTAINING PROBUCOL

BACKGROUND OF THE INVENTION

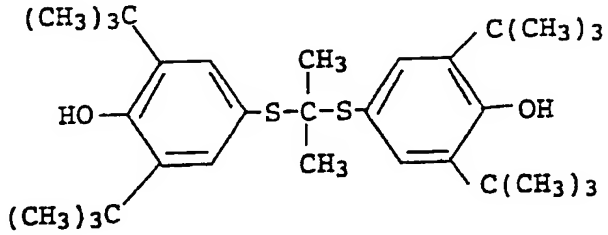
Probucol, a serum cholesterol lowering agent, is presently marketed as Lorelco® 250 and 500 mg tablets. The bioavailability of probucol from tablet dosage form is estimated to be 2-8 percent [J.F. Heeg and H. Tachizawa, Nouv. Presse Med., 9, 2990-2994 (1980)]. This poor bioavailability is most likely caused by the extremely hydrophobic nature of probucol. Several approaches for improving the bioavailability of poorly water soluble drugs have been reported in the literature. Drugs are absorbed from the gastrointestinal tract most rapidly when administered as aqueous solutions. The absorption rate of a drug from an oil solution may be enhanced, however, if the oil is digestible. Therefore, it was considered appropriate to develop an oil solution formulation of probucol filled in a hard gelatin capsule as one of the approaches to improving its bioavailability. In developing such a formulation, it was unexpectedly discovered that one such formulation that increased bioavailability also resulted in reduced variability of plasma drug levels of probucol in a patient population to which the formulation was administered.

SUMMARY OF THE INVENTION

Three new pharmaceutical dosage forms of probucol were prepared and the relative bioavailability was evaluated in man. One of these dosage form, a solution of probucol in Captex® 200 filled in hard gelatin capsules, was found (by extrapolation) to be approximately equal to the Lorelco® 500 tablet at about 1/6 the dose. The solubility of probucol was determined in several natural and derived vegetable oils. Captex® 200, a vegetable oil containing propylene glycol esters of caprylic (C_8) and capric (C_{10}) fatty acids, provided the highest solubility for probucol and was therefore selected as the preferred vehicle for an improved probucol formulation. Also, unexpectedly, there was significantly less variability in probucol plasma drug levels with the Captex® 200 formulation. In view of the increased bioavailability of probucol when administered in the Captex® 200 formulation and in light of the unexpected reduced variability in probucol plasma levels, this formulation is the subject of this application.

DETAILED DESCRIPTION OF THE INVENTION

Probucol is a compound according to Formula I, namely 2,2'-bis (3,5-di-tertiarybutyl-4-hydroxyphenylthio)propane.



FORMULA I

The compounds of Formula I can be prepared as described in U.S. Patents Nos. 3,576,883, 3,786,100, 3,862,332, 3,987,500 and 4,900,757, incorporated herein by reference. More specifically, 2,2'-bis (3,5-di-tertiarybutyl-4-hydroxy phenylthio)propane can be prepared as described in U.S. Patent No. 3,576,883, also incorporated herein by reference. Alternately, this compound can be prepared according to the method set forth in U.S. Patent Nos. 4,734,527 (Kraus) or 4,861,443 (Van Effen), incorporated herein by reference. The indication for probucol is primary hypercholesterolemia. Recent studies in animals have indicated that probucol has a beneficial effect on atherosclerosis independent of cholesterol lowering.

The present invention is directed towards pharmaceutical compositions of probucol dissolved in a propylene glycol ester of fatty acids wherein the fatty acids are selected from the group consisting of the fatty acids represented by $C_xH_{2x}O_2$, wherein x is 4, 6, 8, 10, 12, 14, 16. This group specifically includes butyric acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid and palmitic acid. The most preferred embodiment of the invention is a propylene glycol ester of capric and caprylic acids, known as propylene glycol dicaprylate/dicaprate. Captex® 200 is a specific trade name for propylene glycol dicaprylate/-dicaprate and is supplied by Karlshamns Lipid Specialties USA, P.O. Box 569, Columbus, OH 43216-0569. Reference to Captex® 200 should not be construed as limiting and it will be understood that any reference to Captex® 200 should be construed to generically include all propylene glycol dicaprylates/dicaprates. Propylene glycol dicaprylate/-dicaprate is also known as Neobee 20, supplied by Stepan Co., PVO Dept., 100 W. Hunter Ave., Maywood, NJ 07607, and as Miglyol 840 , supplied by Huls America, P.O. Box 456, Piscataway, NJ 08855-0456. Captex® 300 and Capmul MCM is also supplied by Karlshamns Lipid Specialties USA.

SOLUBILITY DETERMINATION

The solubility of probucol was determined in olive, sunflower, peanut, vegetable, corn, Captex® 200 and 300, and Capmul® MCM oils. Captex® 200 is a propylene glycol ester of caprylic (C_8) and capric (C_{10}) fatty acids obtained by fractionation of certain coconut oil fatty acids and is known generically as propylene glycol dicaprylate/dicaprate. Captex® 300 is a caprylic and capric acid triglyceride obtained by fractionation and subsequent esterification of coconut oil and is known generically as caprylic/capric triglyceride. Capmul® MCM is a mono and diglyceride of caprylic and capric acids.

Eight grams of each oil were transferred into a glass tube with a teflon liner screw cap, and 2.5 g of probucol were added to each tube. The tubes were capped and shaken by hand until the probucol particles were wetted. The tubes were then rotated for at least 48 hours on a test tube rotating apparatus. The solubility of probucol was determined using a high performance liquid chromatography (HPLC) assay procedure.

The solubility values (%w/v) of probucol in various oils are shown in Table I.

TABLE I
SOLUBILITY OF PROBUCOL IN VARIOUS OILS

Oil	Solubility (% w/v)	Oil	Solubility (% w/v)
Peanut	5.6	Corn	5.8
Olive	5.5	Captex® 200	18.2
Sunflower	5.8	Captex® 300	12.5
Safflower	5.9	Capmul® MCM	6.3
Vegetable	5.8		

The highest solubility was observed in Captex® 200 oil. Considering a 50 mg probucol dose, and the constraints on the capsule size and its fill volume, the Captex® 200 was selected for further study. Although coconut oil is known to increase the serum cholesterol level, the literature on Captex® oil indicated that the medium chain fatty acids present in this oil do not contribute to the increase in the cholesterol level. Additionally, there is also evidence that these acids are absorbed through the portal system [V.K. Babayan, Lipids, 22, 417-420 (1987)] and may actually lower the cholesterol level [J.W. Stewart, K.D. Wiggers, N.L. Jacobson, P.J. Berger, Journal of Nutrition, 108, 561-566 (1978) and D. Kritchevsky, S.A. Tepper, Journal of Nutrition, 86, 67-72 (1965)]. Although the exact mechanism of action of probucol is not completely understood, there is speculation that its primary mechanism of action is in the liver. The portal absorption of the fatty acids present in Captex® 200 may be an advantage if probucol is to exercise its action mainly in the liver.

In order to determine if the solubility of probucol could be enhanced by incorporating absolute ethanol in the oil, three binary systems: safflower oil:ethanol (90:10), polyethylene glycol (PEG) 400:ethanol (90:10, 80:20, 70:30), and Captex® 200:ethanol (95:5, 90:10, 85:15, 80:20, and 75:25) were evaluated. The solubility data shown in Table II indicate that in each case the solubility of probucol increased in the presence of ethanol.

TABLE II
SOLUBILITY OF PROBUCOL IN VARIOUS BINARY SOLVENT SYSTEMS

Solvent System	Ratio	Solubility (%w/v)
Safflower Oil:Ethanol	90:10	11.5
PEG 400	100:00	2.8
PEG 400:Ethanol	90:10	5.8
PEG 400:Ethanol	80:20	9.5
PEG 400:Ethanol	70:30	13.1
Captex® 200:Ethanol	95:5	23.0
Captex® 200:Ethanol	90:10	24.0
Captex® 200:Ethanol	85:15	25.0
Captex® 200:Ethanol	80:20	26.0
Captex® 200:Ethanol	75:25	26.0

BIOAVAILABILITY AND SERUM VARIABILITY STUDIES

Further studies were conducted to assess the bioavailability of the experimental formulations of probucol. Two studies were conducted as open, randomized, parallel studies with twelve subjects per treatment group. Lorelco® 500 mg tablets were used as the reference formulation and compared with a Scherer soft gelatin capsule (Protocol A) and Captex® Oil Solution and PEG (polyethylene glycol) 8000 comelt (Protocol B), respectively, each containing 50 mg of probucol.

The current formulation of Lorelco® is 500 mg of probucol in admixture with corn starch, ethylcellulose, glycerine, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, iron oxide, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80, talc and titanium dioxide. PEG 8000 comelt is a mixture of probucol and polyethylene glycol 8000 (PEG 8000 is known in the art). Size two gelatin capsules were filled with 100 mg

of the 50:50 probucol:PEG 8000 comelt, corresponding to a 50 mg dose of probucol. The Scherer soft gel is a mixture of fill weight 310 mg consisting of 50 mg probucol, 208 mg Captex® 200, 26 mg polysorbate 80 and 26 mg Imwitor 742 (caprylic/capric glycerides-HULS America).

Summary statistics (mean, standard deviation, and coefficient of variation) for dose corrected pharmacokinetic parameters are listed in Tables III and IV for Protocols B and A respectively.

TABLE III
PROTOCOL B - Summary Statistics For Dose Corrected Pharmacokinetic Parameters
Mean ± S.D., (C.V.), (N = 12)

Dose Corrected Parameters	Lorelco®	Captex® Oil	PEG 8000
AUC168 (μg*hr ml^{-1})	162 ± 108 (67%)	919 ± 127 (14%)	979 ± 363 (37%)
C_{MAX} (μg/ml)	2.32 ± 1.50 (65%)	13.5 ± 2.72 (20%)	13.9 ± 4.23 (30%)
T_{MAX} (hr)	20.0 ± 7.24 (36%)	18.3 ± 7.13 (39%)	20.0 ± 7.43 (37%)

TABLE IV
PROTOCOL A - Summary Statistics For Dose Corrected Pharmacokinetic Parameters
Mean ± S.D., (C.V.), (N = 12)

Dose Corrected Parameters	Lorelco®	Scherer soft gel
AUC168 (μg*hr ml^{-1})	276 ± 126 (47%)	1017 ± 328 (32%)
C_{MAX} (μg/ml)	3.74 ± 1.55 (41%)	14.2 ± 3.49 (25%)
T_{MAX} (hr)	18.7 ± 6.89 (37%)	19.5 ± 7.14 (37%)

For Protocol B, based on the dose corrected mean AUC (area under the curve) and C_{max} (maximum concentration) values, both Captex® Oil solution and PEG 8000 comelt are estimated to be 5 times or more bioavailable than the Lorelco® 500 mg tablet (Table III). T_{max} values are similar for all three formulations. To make a fair comparison of the variabilities of the test formulations (Captex® Oil Solution and PEG comelt), and the reference formulation (Lorelco® 500 mg tablet), AUC and C_{max} values for Captex® Oil Solution and PEG 8000 comelt were multiplied by 1.76 and 1.65, respectively (these scale factors were used so that all formulations have the same AUC values). Based on the standard deviation of these extrapolated values (Table V) and the coefficient of variation of the raw values (Table III), AUC values of Captex® Oil Solution are approximately 25 and 7 times less variable than the Lorelco® tablet and the PEG 8000 treatment, respectively, and C_{max} values of Captex® Oil Solution are approximately 9 and 2.3 times less variable than the Lorelco® tablet and PEG 8000 treatment, respectively. The variability of PEG 8000 comelt is similar to the Lorelco® 500 mg tablet.

Similar procedures were also used for Protocol A. Based on the dose corrected values, the Scherer soft gel treatment is estimated to be 3.7 times more bioavailable than the Lorelco® 500 mg tablet (Table IV). T_{max} values are similar for both formulations. The variability of Scherer soft gel treatment is similar to the Lorelco® 500 mg tablet (Table V).

TABLE V
Comparison Of Variances With Matched AUC Values
Standard Deviation Of The Extrapolated Values (N=12)

PROTOCOL B

Parameter	Treatment* Lorelco®	PEG 8000	Captex® Oil
AUC168 (μg*hr ml^{-1})	108.2	61.8	22.9
CMAX (μg/ml)	1.50	0.72	0.49
TMAX (hr)	7.20	7.10	7.40

PROTOCOL A

Parameter	Treatment* Lorelco®	Scherer soft
AUC168 (μg*hr ml^{-1})	125.7	86.9
CMAX (μg/ml)	1.55	0.94
TMAX (hr)	6.90	7.10

*Treatments with a common bracket are not significantly different.

EXAMPLE I

Probucol (50.0 mg) was dissolved in propylene glycol esters of caprylic/capric fatty acids [Captex® 200, manufactured and supplied by Karlshamns Lipid Specialties USA, P.O. Box 569, Columbus, OH 43216-0569, as Captex® 200, (283.0 mg) and stirred until a clear solution was obtained. The resulting clear solution was filled into hard gelatin capsules (white opaque gelatin capsule size no. 1, 73 mg) so that each capsule contained an approximate weight of 333.0

mg of solution. The bulk solution was assayed for probucol before filling the capsule and the fill weight was adjusted according to the actual percent of probucol in the solution to provide a 50 mg dose of probucol. Using a capsule banding apparatus, a solution of gelatin (0.647 mg), polysorbate 80 (0.027 mg), and purified water (2.076 mg) was applied to seal the cap to the body of the capsule. The gelatin band was then allowed to harden.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition of probucol adapted to enhance the bioavailability of probucol while reducing plasma probucol level variability in a patient population comprising a therapeutically effective amount of probucol dissolved in a propylene glycol ester of fatty acids wherein the fatty acids are selected from the group consisting of the fatty acids represented by $C_xH_{2x}O_2$, wherein x is 4, 6, 8, 10, 12, 14, 16.

2. A pharmaceutical composition according to claim 1 wherein the fatty acids are selected from the group consisting of the fatty acids represented by $C_xH_{2x}O_2$, wherein x is 6, 8, 10, 12.

3. A pharmaceutical composition according to claim 1 wherein the fatty acids are selected from the group consisting of capric and caprylic acids.

4. Use of a pharmaceutical composition according to any of claims 1-3 to lower serum cholesterol levels.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/08565

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/08 A 61 K 9/48 A 61 K 9/66
A 61 K 47/14 A 61 K 31/10

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	US,A,3862332 (J.W. BARNHART) 21 January 1975, see the claims 1,3,8,11-12; column 12; example 9; column 13, example 14; column 14, example 17 (cited in the application)	1,4
A	US,A,4902513 (J. CARVAIS) 20 February 1990, see the claims; column 4, example XVIII	1,4

° Special categories of cited documents : [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22-01-1992	17. 02. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Danielle van der Haas

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9108565 SA 54190

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The members are as contained in the European Patent Office EDP file on 06/02/92
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3862332	21-01-75	DE-A,B,C 1767443	09-09-71
		FR-M- 8064	06-07-70
		GB-A- 1168193	22-10-69
		NL-A- 6806010	12-11-68
US-A- 4902513	20-02-90	None	

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60/080,273	1 April 1998 (01.04.98)	US

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Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ANTICANCER COMPOSITIONS

(57) Abstract

Pharmaceutical dosage forms for anticancer drugs, and paclitaxel in particular, are described in which the active drug is formulated as storage stable self–emulsifying preconcentrate.

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ANTICANCER COMPOSITIONS

FIELD OF INVENTION

The present invention relates generally to cancer therapeutics. More particularly it is directed to novel pharmaceutical compositions of water insoluble anticancer drugs for therapeutic administration as exemplified by the taxanes which include paclitaxel, docetaxel and their derivatives and analogues.

BACKGROUND AND SUMMARY OF THE INVENTION

Paclitaxel is a taxane and a member of the terpenoid family of compounds present in very small quantities in the Taxus brevifolia species such as the pacific Yew tree. These compounds, collectively known as taxoids, taxins or taxanes, have potent anticancer properties in, among others, ovarian cancer, lymphoma, and breast cancer. Because of its poor solubility in water, the current commercial formulation of paclitaxel is prepared by dissolving 6 mg of the drug in one milliliter of a mixture of polyoxyethylated castor oil (Cremophor®(EL) and dehydrated alcohol. The commercially available paclitaxel formulation is for intravenous administration only. There exists no commercial formulation of paclitaxel, which can be administered orally. The commercial injectable formulation is physically unstable especially for treatments requiring long infusion time. The infusate may contain up to 10% each of alcohol and Cremophor®EL. The physical stability of the paclitaxel formulation may be increased by increasing the amounts of Cremophor®EL in the formulation, but may also lead to an increased incidence of adverse reactions. Yet another approach as described in U.S. patent 5,681,846 is to decrease the drug and Cremophor® concentration and increase the alcohol content in the formulation.

An undesirable effect of Cremophor®EL in paclitaxel and other drug formulations is the production of possible anaphylactoid reaction with associated dyspnea, hypotension, angioedema and uticaria. Cremophor®EL is also known to extract plasticizers such as di-ethylhexyl-phthalate from the polymers commonly used intravenous infusion tubings and infusion bags. These plasticizers are known to promote toxic reactions, such as Adult Respiratory Distress Syndrome (ARDS), in patients which have been exposed to high levels.

Various other methods have been used to increase the water solubility of paclitaxel and other anticancer drugs, for example, by conjugation of the water insoluble drug moiety with

water soluble polymers as taught by U.S. patent 5,437,055, WO 97/10849, and WO 97/33552. While WO 94/12031 teaches that a composition of paclitaxel with Cremophor®EL, absolute alcohol and citric acid increases the stability however, no mention is made if the proposed composition increases the solubility of paclitaxel. Others have used liposome preparations as a means of eliminating Cremophor®EL and reducing vehicle toxicity as described by Sharma et al (Pharm. Res. 11:889-896, 1994). An oil-in-water emulsion (U.S. patent 5,616,330) is another approach to preparing Cremophor® free paclitaxel formulation. The latter two formulation approaches have limitations in terms of low degree of drug loading. Yet another approach uses cyclodextrins to make a water-soluble formulation of paclitaxel as described in WO 94/26728.

The present invention is based on a strong need for a safer and stable injectable and oral formulation of anticancer drugs, particularly the taxanes such as paclitaxel, docetaxel and their derivatives and analogues and other anticancer drugs.

U.S. patent 5,407,683 discloses a composition containing paclitaxel in squalene as solution in absence of a surfactant and then forming a self-emulsifying glass by addition of an aqueous sucrose solution followed by evaporation of water. The resulting glass upon mixing with water forms an emulsion with a particle size in a range of 2 to 10 μm. The preparation of such glass requires the use of undesirable organic solvents, which must be completely removed before medical use.

Quay et al describe a conventional oil-in-water emulsion system (WO 98/30205) consisting of vitamin E as a carrier oil in which a drug may be dissolved, together with polyethyleneglycol and related surfactants. Conventional emulsions have limited shelf life and are often difficult to terminally heat sterilize or even filter sterilize. The particle size of conventional emulsions is usually far greater than microemulsions.

Microemulsions are thermodynamically stable and optically transparent or opaque depending on the particle size of the emulsion. Microemulsions have a mean droplet size of less than 200 nm, in general between 20-100 nm. In contrast to conventional emulsions, the microemulsions are formed in the presence of an aqueous phase by self emulsification without any energy input. In the absence of water, this self emulsifying system exists as a transparent-looking mixture of oil and surfactants in which a lipophilic drug is dissolved.

Wheeler et al describe an emulsion preparation (U.S. patent 5,478,860) containing a mixture of paclitaxel, an oil and a polyethylene glycol-linked lipid which is covered by a

monolayer of a polar lipid such as phosphatidylglycerol or phosphatidylethanolamine. This mixture, after homogenization in presence of an aqueous phase at appropriate pressure, yields an emulsion with a particle size in the range of 100 nm. It is not known if this is the mean or minimum particle size and if it is number weighted or volume weighted. The necessity of using undesirable organic solvents for initial dissolution of ingredients is not advisable even if the organic solvent is removed prior to use. In addition to an elaborate evaporation step, the method requires input of energy by way of high pressure homogenization adding to the overall cost. Because the preconcentrate of a true microemulsion is usually non-aqueous, it can provide longer shelf life than a regular emulsion which is in aqueous suspension.

Lacy et al disclose a capsule delivery system (U.S. patent 5,645,856) for oral delivery of hydrophobic drugs containing a digestible oil, and a combination of surfactants. The selection of surfactant is made such that it inhibits the in vivo lipolysis of the oil.

Eugster discloses an ultra microemulsion system (Swiss Patent CH 688 504 A5) for paclitaxel and its analogs composed of an oil and one or more surfactants providing a formulation of the drug with a mean particle size of 2.2-3 nm thus approaching a solution rather than an emulsion. It is not known if this formulation is useful for oral, injectable or topical use.

There have been attempts to enhance oral activity of taxanes by co-administration of taxanes with another drug such as cinchonine (WO 97/27855) or cyclosporin, ketoconazole etc. (WO 97/15269). Similarly, WO 97/48689 describes the use of various carbocyclic compounds in combination with anticancer drugs to enhance oral bioavailability of the drug. All three of these approaches have the drawback of combination drug therapy where a second drug with drastically different pharmacological activity is administered. In practice such a drug combination approach is the last resort taken by those familiar with the drug development process due to drastic increase in preclinical and clinical regulatory requirement for approval resulting in increasing cost and time to market.

SUMMARY OF THE INVENTION

In accordance with the present invention it has now surprisingly been found that particularly stable anticancer drug formulations, particularly the taxanes, that self emulsify in aqueous medium giving an average particle size in a range of about 10 nm to about 10 microns and that have improved bioavailability characteristics, are obtainable. Also described are self-

emulsifying preconcentrates that disperse, without the input of high energy (i.e., other than mixing energy to cause dispersion), to form droplets of average size of up to about 10 microns.

Accordingly, this invention provides a pharmaceutical composition in the form of a self-emulsifying preconcentrate comprising an anticancer drug as the active ingredient solubilized in a carrier medium comprising at least one hydrophobic component, at least one hydrophilic component and at least one surfactant.

The self-emulsifying systems and their corresponding preconcentrates described in this invention consist of a hydrophobic component, an ingredient selected from triglycerides, diglycerides, monoglycerides, free fatty acids, and fatty acid esters (such as fatty acid esters of hydroxyalkanes or of dihydroxyalkanes) and derivatives thereof, individually or in combination. Preferably the surfactant is a non-ionic surfactant or a mixture of non-ionic surfactants. The invention is also characterized as optionally including a hydrophilic component, for instance a hydroxyalkane such as ethanol and/or a dihydroxyalkane such as 1,2-propylene glycol and/or a polyethylene glycol having an average molecular weight of less than or equal to 1000.

Compositions of the current invention will include, in addition to the water insoluble drug, the hydrophobic components and the optional hydrophilic components, and at least one surfactant. Examples of suitable surfactants are:

1. Polyoxyethylene-sorbitan-fatty acid esters; e.g. mono- and tri-lauryl, palmityl, stearyl and oleyl esters; e.g. products of the type known as polysorbates and commercially available under the trade name "Tween".

2. Polyoxyethylene fatty acid esters, e.g., polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj.

3. Polyoxyethylene castor oil derivatives, e.g., products of the type known and commercially available as Cremophors®. Particularly suitable are polyoxyl 35 castor oil (Cremophor® EL) and polyoxyl 40 hydrogenated castor oil (Cremophor® RH40).

4. α-tocopherol, α-tocopheryl polyethylene glycol succinate (vitamin E TPGS), α-tocopherol palmitate and α-tocopherol acetate .

5. PEG glyceryl fatty acid esters such as PEG-8 glyceryl caprylate/caprate (commercially known as Labrasol), PEG-4 glyceryl caprylate/caprate (Labrafac Hydro WL 1219), PEG-32 glyceryl laurate (Gelucire 44/14), PEG-6 glyceryl mono oleate (Labrafil M 1944 CS), PEG-6 glyceryl linoleate (Labrafil M 2125 CS).

6. Propylene glycol mono- and di-fatty acid esters, such as propylene glycol laurate, propylene glycol caprylate/caprate; also diethyleneglycol-monoethylether (DGME), commercially known as Transcutol (Gattefosse, Westwood, NJ).

7. Sorbitan fatty acid esters, such as the type known and commercially available under the name Span (e.g., Span 20).

8. Polyoxyethylene-polyoxypropylene co-polymers, e.g., products of the type known and commercially available as Pluronic or Poloxamer.

9. Glycerol triacetate.

10. Monoglycerides and acetylated monoglycerides, e.g., glycerol monodicocoate (Imwitor 928), glycerol monocaprylate (Imwitor 308), and mono-and di-acetylated monoglycerides.

Suitable surfactants are not limited to those mentioned above, but may include any compound or compounds that would enhance the galenic properties of the preconcentrate.

Compositions in accordance with the present invention may include other ingredients in addition to the drug, one or more hydrophobic components, one or more hydrophilic components, one or more surfactants, inhibitors of cytochrome P450 enzymes or inhibitors of the p-glycoprotein transport system such as grapefruit extract or compounds isolated from it. The composition may include, in addition to the forgoing, one or more ingredients, additives or diluents such as pharmaceutically acceptable polymeric or inorganic materials, anti-oxidants, preserving agents, flavoring or sweetening agents and so forth.

Compositions in accordance with the present invention may be liquid or solids at ambient temperature. They may be filled in soft or hard gelatin capsules in the form of liquid composition, molten composition, or granules or powder (if composition is solid at ambient temperature and was cooled and processed before filling). Coating may be also applied to capsules or tablets. The preconcentrate may be also be diluted with water to obtain stable emulsions that may be employed as drinking formulations, or packaged as such for injection after appropriate dilution with an aqueous medium, for example.

DETAILED DESCRIPTION OF THE INVENTION

A self-emulsifying preconcentrate of the present invention comprising an anticancer drug must contain a hydrophobic component, a surfactant and optionally a hydrophilic component. The surfactant and hydrophilic component are needed for the composition to form in aqueous medium a self-emulsifying system having an average particle size of between about

10 nm and about 10 microns. They may also help enhance the solubility and stability of the anticancer drug in the formulation. The hydrophobic component is needed because if it is not incorporated in appropriate amounts in the formulation, precipitation of the drug will be observed upon mixing of the composition with an aqueous medium and/or on storage. Similar observations may be made for the hydrophilic and surfactant components.

Based on the above, appropriate combinations or mixtures of a hydrophobic component, a surfactant and a hydrophilic component (when used) with the water insoluble drug are necessary to obtain a stable microemulsion preconcentrate that would yield upon mixing with an aqueous medium a stable dispersion with an average particle size of between about 10 nm and about 10 microns.

Preferred as hydrophobic components are triglycerides, diglycerides, monoglycerides, free fatty acids, and fatty acid esters and derivatives thereof, individually or in combination. Examples of hydrophobic components include but are not limited to propylene glycol dicaprylate/caprate, caprilic/capric triglyceride, caprylic/capric/linoleic triglyceride, e.g. synthetic medium chain triglycerides having C8-12 fatty acid chains or other derivatized (synthetic) triglycerides of the type known and commercially available under Miglyol 810, 812, 818, 829 and 840, linoleic acid, linoleic acid ethyl ester, fish oils as free fatty acids, their esterification and their transesterification products, e.g. of the type known and commercially available under EPAX 6000 FA, EPAX 4510 TG, individually or in combination. Additional examples include vegetable oils and C12-18 fatty acid mono-, di- and triglycerides prepared by individual admixing or as transesterification products of vegetable oils (such as soybean oil, almond oil, sunflower oil, olive oil or corn oil) with glycerol.

Preferred as hydrophilic components are 1,2-propylene glycol, ethanol and polyethylene glycol having an average molecular weight of less than or equal to 1000, individually or in combination. More preferred as hydrophilic components are 1,2-propylene glycol and ethanol, individually or in combination. Especially preferred as hydrophilic components is a combination or mixture of 1,2-propylene glycol and ethanol.

The relative proportion of the drug and the other ingredients in the composition of the current invention will vary depending whether it is delivered as a self-emulsifying preconcentrate or after dilution with water, depending on the particular ingredients and the desired physical properties of the formulation. Especially desired concentration limits in the self-emulsifying preconcentrate are as follows:

1. Oil phase: from 10 to 80% w/w of the preconcentrate. The oil phase may consist of triglycerides, diglycerides, monoglycerides, free fatty acids, propylene glycol mono or diesters and free fatty acids, esters and derivatives thereof, individually or in combination.

2. Cumulative amounts of surfactants: from 20 to 80% w/w of the preconcentrate.

3. Cumulative amounts of hydrophilic components, such as 1,2-propylene glycol and/or ethanol and/or a polyethylene glycol having an average molecular weight of less than or equal to 1000 : from 0% to 40% w/w of the preconcentrate. The total of all ingredients will be 100%.

It is understood that the application of the teachings of the present invention, to the conditions described, will be evident to one skilled in the art of preparing such formulations, and to one skilled in treating such medical conditions. Additional features and advantages of the present invention are described below in preferred embodiments, which are intended as example, and not as limitation. In the following examples, the ingredients were weighed out into appropriate containers in the amounts described below. In all examples described below, a clear liquid was obtained upon appropriate mixing and heating.

EXAMPLES

The formulations represented in the following examples were prepared by mixing the oil components with surfactants and cosurfactants followed by the addition of drug powder as indicated. The composition may be prepared at room temperature or heated to 40-50°C to accelerate the solubilization process. Several mixing techniques can be used ranging from mechanical stirring and agitation to sonication. All compositions shown below give liquid or semi-solid preconcentrates at room temperature.

An experiment to test the efficiency of forming microemulsions from the preconcentrates was carried out by diluting the preconcentrate in 20-50 fold with water or simulated gastric fluid with gentle mixing or shaking. The aqueous medium temperature varied between 20 and 37°C. Particle size analysis was then carried out using a photon correlation spectroscopy based particle sizer, Nicomp 370. Data reported in the following examples correspond to volume weighted particle size.

EXAMPLE 1

Ingredients	Amount (g)
Miglyol 840	1.971
Cremophor® RH40	2.190
Imwitor 308	0.767
Labrasol	0.548
Paclitaxel	0.175
Total	5.651

Mean particle size: 31 nm

EXAMPLE 2

Ingredients	Amount (g)
Miglyol 840	4.820
Cremophor® RH40	4.990
Imwitor 308	1.750
Labrasol	1.250
Paclitaxel	0.489
Transcutol	2.000
Total	15.299

Mean particle size: 13 nm

EXAMPLE 3

Ingredients	Amount (g)
Miglyol 840	1.396
Cremophor® RH40	1.551
Imwitor 308	0.543
Labrasol	0.388
Paclitaxel	0.122
Grapefruit extract	0.400
Total	4.400

Mean particle size: 30 nm.

EXAMPLE 4

Ingredients	Amount (g)
Miglyol 840	1.560
Cremophor® RH40	1.610
Imwitor 308	0.565
Labrasol	0.405
Paclitaxel	0.285
Ethanol	0.575
Total	5.000

Mean particle size: 14 nm

EXAMPLE 5

Ingredients	Amount (g)
Miglyol 812	1.435
Tween 80	2.150
Lipoid E80	0.705
Soybean oil	0.178
Linoleic acid	0.174
Ethanol	0.305
Paclitaxel	0.068
Total	5.000

Mean particle size: 102 nm

EXAMPLE 6

Bioavailability of paclitaxel micro-emulsion preconcentrate was assessed using the formulation described in Example 1. Paclitaxel was given in doses of 2.5 mg/Kg or 5 mg/Kg to 8 male dogs of approximately 10 Kg body weight. The formulation was administered in the morning after overnight fasting in the form of a capsule followed by water. Free access to food and water was allowed two hours after dosing. Blood samples were drawn at different point (pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr) and stabilized with EDTA, placed in Vacutainers, and stored at 2-8°C. The blood samples were then extracted using a liquid-liquid method and assayed by HPLC/UV. Bioavailability calculations were done by comparing the pharmacokinetic (PK) profiles obtained for orally given paclitaxel micro-emulsion preconcentrate with an intravenous commercial formulation. Bioavailability values ranging from 25 % to 60 % were obtained. Figure 1 corresponds to a typical pharmacokinetic profile obtained for paclitaxel preconcentrate.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not to be limited to the disclosed embodiment, but on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an anticancer drug as active ingredient dissolved in a carrier system comprising at least one hydrophobic component, a hydrophilic component and at least one surfactant, wherein the hydrophobic component is selected from triglycerides, diglycerides, monoglycerides, free fatty acids, and fatty acid esters and derivatives thereof, individually or in combination and wherein the hydrophilic component is a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of less than or equal to 1000 or mixtures thereof.

2. A pharmaceutical composition consisting essentially of a taxane dissolved in a carrier system composed of a surfactant, a hydrophobic component comprising a triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester or mixtures thereof and hydrophilic phase comprising a hydroxyalkane, a dihydroxyalkane, polyethylene glycol having a molecular weight of at most 1000.

3. The composition of claim 1 or claim 2 wherein the hydrophobic component is a fatty acid ester of a hydroxyalkane, a fatty acid ester of a dihydroxyalkane, a fatty acid mono-, di- or triglyceride or a transesterification product of a vegetable oil with a glycerol.

4. The composition of claim 1 or claim 2 wherein the hydrophilic component is 1,2-propylene glycol, ethanol, a polyethylene glycol or mixtures thereof.

5. The composition of claim 1 or claim 2 wherein at least one surfactant is non-ionic.

6. The composition of claim 1 or claim 2 further including an inhibitor of P-glycoprotein transport system or an inhibitor of P450 enzymes.

7. The composition of claim 6 wherein the inhibitor is grapefruit extract or a component thereof.

8. A storage-stable self-emulsifying preconcentrate of an anticancer drug in a microemulsion composed of:

10 to 80% w/w of a hydrophobic component of at least one triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester, fish oil, vegetable oil or mixtures thereof; 20 to 80% w/w of surfactant phase comprising at least one non-ionic surfactant,

0-35% w/w diethylene glycol monoethylether, and

0 to 40% w/w of at least one hydrophilic component selected from a hydroxyalkane,

dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and mixtures thereof

wherein said preconcentrate, when mixed with an aqueous medium, gives an average particle size of at most 10 microns.

9. The self-emulsifying preconcentrate of claim 8 containing from 15 to 75% w/w hydrophobic component.

10. The self-emulsifying preconcentrate of claim 8 containing from 20 to 80% w/w surfactant.

11. The self-emulsifying preconcentrate of claim 8 containing up to 30% w/w hydrophilic component.

12. A storage-stable, self-emulsifying, clear, liquid preconcentrate of at least one taxane consisting essentially of:

10 to 80% w/w of a hydrophobic component of at least one triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester, fish oil, vegetable oil or mixtures thereof;

20 to 80% w/w of surfactant phase comprising at least one non-ionic surfactant, and

up to 40% w/w of at least one hydrophilic component selected from a hydroxy alkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and mixtures thereof

wherein said preconcentrate, when mixed with an aqueous medium, gives an average particle size of at most 10 microns, or which upon oral administration forms *in situ* a microemulsion in the gastrointestinal tract.

13. The liquid preconcentrate of claim 12 wherein the hydrophilic component is selected from 1,2-propylene glycol, ethanol, polyethylene glycol having an average molecular weight of less than or equal to 1000 and combinations thereof.

14. The liquid preconcentrate of claim 13 wherein the hydrophilic component is present and is a mixture of 1,2-propylene glycol and ethanol.

15. The liquid preconcentrate of claim 12 containing up to 30% w/w hydrophilic component.

16. The liquid preconcentrate of claim 12 wherein the hydrophobic component is a fatty acid ester of a hydroxyalkane, a fatty acid ester of a dihydroxyalkane, a fatty-acid mono-, di- or tri-glyceride or a transesterification product of a vegetable oil with a glycol.

17. An orally administrable pharmaceutical composition consisting essentially of the preconcentrate of claim 12 in a pharmaceutically acceptable carrier or diluent.

18. A parenterally injectable pharmaceutical composition consisting essentially of the preconcentrate of claim 12 in a pharmaceutically acceptable diluent.

19. A method of orally or parenterally administering an anticancer drug to a subject in need of same comprising storage-stable, self-emulsifying preconcentrate of a solubilized anticancer drug composed of:

10 to 80% w/w of a hydrophobic component of at least one triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester, fish oil, vegetable oil and mixtures thereof;

20 to 80% w/w of surfactant phase comprising at least one non-ionic surfactant, and

up to 40% w/w of at least one hydrophilic component selected from a hydroxy alkane, a dihydroxy alkane, a polyethylene glycol having an average molecular weight of at most 1000, and mixtures thereof

wherein said preconcentrate, when mixed with an aqueous medium, gives an average particle size of at most 10 microns.

20. A method of orally administering a self-emulsifying preconcentrate of claim 12 comprising a taxane solubilized in a stable, self-emulsifying system which self-disperses in water, simulated intestinal, or simulated gastric fluid to yield a homogeneous phase with a particle size of below 10 microns.

21. A method of enhancing the oral bioavailability of a taxane comprising solubilizing a taxane in a stable, self-emulsifying system which upon administration forms *in situ* a microemulsion in the gastrointestinal tract.

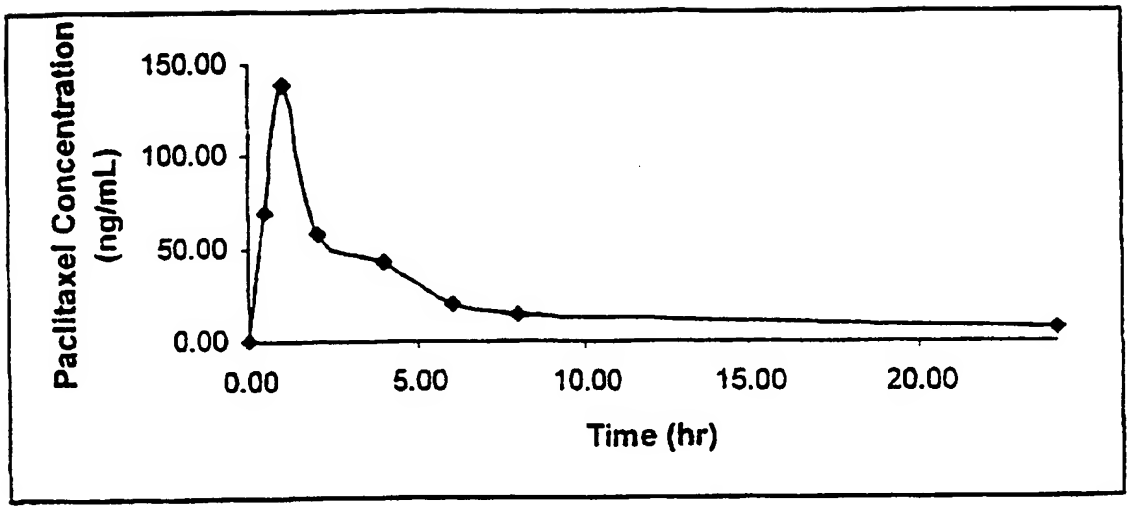
Paclitaxel Concentration (ng/mL)
150.00
100.00
50.00
0.00
0.00
5.00
10.00
15.00
20.00
Time (hr)

FIGURE 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07162

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/107 A61K31/335 A61K47/26 A61K47/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 02247 A (HEMAGEN PFC) 1 February 1996 (1996-02-01) abstract page 1, line 2 - page 3, line 7 page 3, line 12 - page 5, line 20 page 7, line 17 - line 18 page 7, line 23 - line 24 claims 1-36 --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 1999	10. 09. 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Taylor, G.M.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/07162

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LUNDBERG, B.B.: "A Submicron Lipid Emulsion Coated with Amphipathic Polyethylene Glycol for Parenteral Administration of Paclitaxel (Taxol)" J. PHARM. PHARMACOL., vol. 49, 1997, page 16-21 XP002111265 abstract page 16, column 1 - column 2 see page 18: "Design and Characterisation of Drug-Emulsion" see pages 18-19: "Paclitaxel Uptake and Cytotoxicity"	1-18
Y	LIAU-CHU M. ET AL.: "Mechanism of Action of Anaphylactoid Reacitons: Improper Preparation of High-Dose Intravenous Cyclosporine leads to Bolus Infusion of Cremophor EL and Cyclosporine" ANN. PHARMACOTHER., vol. 31, 1997, pages 1287-1291, XP002111266 abstract	1-18
Y	MICHAUD L B: "Methods for preventing reactions secondary to Cremophor EL [comment]" ANNALS OF PHARMACOTHERAPY, vol. 31, no. 11, November 1997 (1997-11), pages 1402-1404, XP002099306 ISSN: 1060-0280 the whole document	1-18
A	WO 98 07434 A (SUPRATEK PHARMA INC ;ALAKHOV VALERY Y (CA); KABANOV ALEXANDER V (U) 26 February 1998 (1998-02-26) abstract examples 1-4 claims 1-11	1-18
A	US 5 560 931 A (EICKHOFF W MARK ET AL) 1 October 1996 (1996-10-01) abstract column 1, line 7 - line 14 column 1, line 50 - line 61 examples 1-4 claims 1-6	1-18

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/07162

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 19-21
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 19-21

Claim 19 is wholly unclear as it attempts to define a method in terms of a product.

Present claims 20 and 21 relate to a product defined by reference to a desirable characteristic or property, namely

"... stable, self-emulsifying system which self-disperses in water, simulated intestinal, or simulated gastric fluid to yield a homogeneous phase with a particle size of below 10 microns" (claims 20);

"... stable, self-emulsifying system which upon administration forms in situ a microemulsion in the gastrointestinal tract"

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely the subject-matter of claims 1-18.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/07162

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 690299 B	23-04-1998
		AU 2872095 A	16-02-1996
		CA 2194226 A	01-02-1996
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WO 9807434 A	26-02-1998	AU 3978497 A	06-03-1998
US 5560931 A	01-10-1996	AU 4862796 A	27-08-1996
		CA 2207304 A	15-08-1996
		EP 0808154 A	26-11-1997
		JP 10513200 T	15-12-1998
		WO 9624332 A	15-08-1996